Investigation of the efficacy of clinoptilolite in calves with cryptosporidiosis

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SUMMARY

This study aims to investigate the efficacy of clinoptilolite in calves infected with *Cryptosporidium*. For this purpose, 30 animals monoinfected with *Cryptosporidium* and 10 healthy calves as a control group were included in the study, and in total four groups were formed. Fluid therapy was administered to all three groups to correct dehydration and acidosis of the calves. Clinoptilolite was administered to the first group at an oral dose of 1 g/day and an oral dose of 1 g/day and standard treatment was applied to the second group. The third group was treated with only standard treatment. Blood gas (pH, HCO_3^-, Na^+, Cl^-, K^+, Crea, BE) and blood biochemistry (AST, ALT, BUN, Glucose) measurements and feces scoring by inspection method (1=watery, 2=pudding consistency, 3=soft, 4=hard) were applied to the study groups. Statistical evaluation of the variables examined in the calves was made in SPSS 24.0 package program. In the second group, there was a significant increase in pH, HCO_3^- ($p < 0.05$) and BE ($p < 0.01$) compared to the first group, while a significant decrease in K^+ ($p < 0.05$) value was detected. In the second group, increase in Na^+, BE values ($p < 0.05$), and a significant decrease in K^+ value ($p < 0.05$) compared to the third group were observed. There was no significant difference among the groups in blood biochemistry results ($p > 0.05$). Feces scores of calves with diarrhea after treatment were statistically improved at $p < 0.05$ level in Groups 1 and 3, and at $p < 0.01$ level in Group 2. It was determined that there were 4 calves in the first group, 9 calves in the second group, and 7 in the third group which showed signs of improvement. As a result, it was concluded that, in addition to standard treatment, the inclusion of clinoptilolite at a daily dose of 1 g/kg orally for 5 days can contribute to the treatment of calves with *Cryptosporidium*, and that it is safe to be used on calves.

KEY WORDS

Cryptosporidium, clinoptilolite, calf.

INTRODUCTION

Zeolites have unique structures that can easily replace other molecules and cations with their negatively charged channels and positively charged alkali spaces. The most common zeolite mineral assemblages in nature are tuffs containing zeolite clinoptilolite and mordenite. The use of clinoptilolite-based products in veterinary and human medicine has increased in recent years due to its many positive medicinal properties such as ion exchange and adsorption capacity[1].

Calf diarrhea is one of the leading neonatal period diseases, which is one of the important problems in calf breeding. The four most important factors reported in the world in calf diarrhea are rotavirus, coronavirus, *Cryptosporidium parvum* (*C. parvum*), and *Escherichia coli* (*E. coli*)[2]. Cryptosporidiosis is a zoonotic infection caused by protozoans of the genus *Cryptosporidium* in mammals, reptiles, poultry, and fish. *C. parvum* is known to be the most disease-causing species in vertebrate animals and humans[3]. Although the life cycle of *C. parvum* is similar to cyst-forming microorganisms such as Toxoplasma and Eimeria, it is formed in *Cryptosporidium* in oocyst sporulation and thus is excreted with feces and shows infective characteristics[4]. Transmission occurs by oral ingestion of oocysts with food or water. It has been reported in aerosol transmission. The fact that oocysts can survive for an average of 6 months at 20 °C in the external environment and are resistant to disinfectants is an important factor in the spread of infection[5]. *C. parvum* is one of the most common pathogenic agents found in calves less than 3 weeks old. The disease, with symptoms such as severe diarrhea, dehydration, weight loss, and slow growth, causes death and serious economic losses[6]. Various anti-*cryptosporidium* (halofuginone lactate, spiramycin, lasalocid) effective substances have been used in its treatment, but with limited success[5]. In this context, new treatment options are needed for cryptosporidiosis.

Studies on the use of clinoptilolite in the treatment of enteric protozoa are limited in our country. It has been determined that

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different concentrations of nanoparticles containing clinoptilolite of *Cryptosporidium*, which causes diarrhea in humans and many animal species, have anti-*cryptosporidium* properties during in vitro infection[7]. Also, Ural et al. used oral clinoptilolite for Giardiasis control in goat kids in their study in 2017[8]. In this study, it was aimed to investigate the effectiveness of clinoptilolite in diarrhea caused by *Cryptosporidium* with high mortality and morbidity in calves.

MATERIALS AND METHODS

The animal material of the study was composed of 30 calves with acute diarrhea and 10 healthy calves 7-30 days. They were of various breeds and sexes and were in public-owned enterprises in the Küçük Menderes region between September and December 2020. *G. duodenalis*, Coronavirus, Rotavirus, *Cryptosporidium*, and *E. coli* K99sp. antigens were screened through rapid test kits (Anigen Rapid Bovid-5 Ag Test Kit, Bionote Lab.) for the differential diagnosis of some infectious agents causing diarrhea. Thirty animals monoinfected with *Cryptosporidium* from a total of 116 animals suffering from acute diarrhea and 10 healthy calves as a control group were included in the study. *Cryptosporidium* positive calves were randomly divided into three groups with n=10 in each group. To correct the dehydration and acidosis of the calves in all three groups, fluid therapy was applied within the first 24 hours. Clinoptilolite treatment dose was determined as 1 g/kg[9]. Afterward, clinoptilolite was administered orally at a dose of 1 g/kg for 5 days to the 1st group, the 2nd group was given clinoptilolite at a dose of 1 g/kg orally and drug treatment (Aminosidin 70 mg/kg orally once a day for 5 days, Meloxicam® 0.5 mg/kg IV single dose), and the third group received drug treatment (Aminosidin 70 mg/kg orally once a day for 5 days, Meloxicam® 0.5 mg/kg IV single dose). The 4th group consisted of n = 10 healthy calves. Feces scoring (1=watery, 2=pudding consistency, 3=soft, 4=hard) was performed on the 1st and 5th days of the study from all groups. For blood gas, blood was taken from V. Jugularis into 2 ml blood gas injector according to the procedure and without waiting, and pH, bicarbonate (HCO_3^-), sodium (Na^{++}), chlorine (Cl^-), potassium (K^+), creatine (Crea), and Base Excess (BE) levels were measured in the blood gas device (Alere Epoc, Germany). For blood biochemistry, 5 ml of blood was taken from Jugular V. into tubes without anticoagulant and was centrifuged at 3000 rpm for 10 minutes. Serums were stored at -20° until measurements were made. Then AST (U/L), ALT (U/L), BUN (mmol/L) and glucose measurements were taken in the biochemistry device (Spotchem EZ SP-4430, Japan).This study was carried out with the approval of the Dokuz Eylül University Animal Experiments Local Ethics Committee, dated 12.08.2020, numbered 25/2020.

Statistical analysis

The normality of distribution of continuous variables was tested by Shaphiro Wilk test. One-way ANOVA and LSD test (for normal data) and Kruskal Wallis and Dunn multiple comparison tests (for non-normal data) were used to compare numerical data across the three groups. Paired t test (for normal data) and Wilcoxon test (for non-normal data) were performed as before-after comparisons. Statistical analysis was performed with SPSS for Windows version 24.0 and a $P< 0.05$ was accepted as statistically significant.

RESULTS

Study results are summarized in Tables 1-3. Four out of 10 animals in group 1 treated only with clinoptilolite, 9 out of 10 animals in group 2 treated with clinoptilolite and drug treatment together, 7 out of 10 animals in group 3 treated with medica-

Table 1 - Blood gas values of diarrheal calves before, after treatment and statistical comparison between groups.

Parameters	Group 1		Group 2		Group 3		Group 4
	B.T (n= 10)	A.T (n= 4)	B.T (n= 10)	A.T (n= 9)	B.T (n= 10)	A.T (n= 7)	(n=10)
pH	7.03 ± 0.08	7.22 ± 0.06	7.01 ± 0.1	7.28 ± 0.05	7.03 ± 0.08	7.3 ± 0.02	7.31 ± 0.03
HCO_3^-	12.48 ± 1.7	21.34 ± 5.48	13.36 ± 1.28	25.97 ± 3.29	13.41 ± 1.46	27.11 ± 2.2	25.68 ± 1.92
Na^+ (mmol/L)	133.51 ± 2.22	139.28 ± 2.85	134.92 ± 2.78	140.44 ± 1.23	135.83 ± 1.62	138.12 ± 2.01	138.63 ± 3.81
Cl^- (mmol/L)	95.83 ± 2.85	101.8 ± 1.17	97.5 ± 0.84	100.54 ± 1.62	97.14 ± 1.34	101.61 ± 1.27	102.29 ± 1.07
K^+ (mmol/L)	6.22 ± 0.06	5.08 ± 0.09	6.01 ± 0.2	4.93 ± 0.02	6.18 ± 0.12	5.02 ± 0.1	4.21 ± 0.11
Crea (mg/dL)	1.66 ± 0.07	0.67 ± 0.04	1.68 ± 0.05	0.6 ± 0.06	1.68 ± 0.07	0.62 ± 0.05	0.71 ± 0.06
BE	-15.74 ± 3.8	3.72 ± 5.4	-15.36 ± 3.41	5.71 ± 0.23	-14.82 ± 3.99	5.64 ± 3.47	5.68 ± 1.08
Statistical Evaluation							
			In-Groups		Between Groups		
	Group 1		Group 2	Group 3	Group 1/Group 2		Group 2/Group 3
pH	*		**	**	*		N.S
HCO_3^-	*		**	*	*		N.S
Na^+ (mmol/L)	*		**	**	N.S		*
Cl^- (mmol/L)	*		**	*	N.S		N.S
K^+ (mmol/L)	*		**	*	*		*
Crea (mg/dL)	**		**	**	N.S		N.S
BE	*		**	*	**		*

N.S: Not Significant, * : P < 0.05, ** : P < 0,01, B.T: Before Treatment, A.T: After Treatment.

Table 2 - Blood biochemistry values of diarrheal calves before, after treatment and statistical comparison between groups.

Parameters	Group 1		Group 2		Group 3		Group 4
	B.T (n= 10)	A.T (n= 4)	B.T (n= 10)	A.T (n= 9)	B.T (n= 10)	A.T (n= 7)	(n=10)
AST (U/L)	152.1 ± 40.2	42.2 ± 5.31	125.2 ± 27.7	43.11 ± 6.95	141.8 ± 36.58	45.14 ± 4.14	44.8 ± 2.49
ALT (U/L)	29 ± 6.93	12.2 ± 1.48	26.2 ± 4.61	12.89 ± 2.98	27 ± 5.46	11.71 ± 2.14	14.8 ± 2.35
BUN (mg/dL)	44.86 ± 4.5	5.78 ± 0.69	45.5 ± 3.65	5.61 ± 1.15	44.32 ± 4.39	6 ± 0.96	5.23 ± 1.1
Glucose (g/dL)	54.2 ± 10.75	74.6 ± 1.14	63 ± 6.57	73.89 ± 1.45	58.8 ± 9.89	74.71 ± 1.98	70 ± 6.48

Statistical Evaluation					
	In-Groups			Between Groups	
	Group 1	Group 2	Group 3	Group 1/Group 2	Group 2/Group 3
AST (U/L)	*	**	*	N.S	N.S
ALT (U/L)	*	*	*	N.S	N.S
BUN (mg/dL)	**	**	**	N.S	N.S
Glucose (g/dL)	*	**	*	N.S	N.S

N.S: Not Significant, * : P < 0.05, ** : P < 0,01, B.T: Before Treatment, A.T: After Treatment.

tion alone showed improvement at the end of the study. Group results of diarrheal calves according to blood gas values before and after treatment are as follows: In Group 1 (clinoptilolite) calves, a significant increase ($p < 0.05$) was determined in blood pH, HCO_3^-, Na^+, Cl^-, BE values after treatment, while a significant decrease in K^+ and Crea values ($p < 0.05$, $p < 0.01$) was detected. In group 2 (clinoptilolite+drug) calves showed a significant increase ($p < 0.01$) in blood pH, HCO_3^-, Na^+, Cl^-, BE values after treatment, and a significant decrease ($p < 0.01$) in K^+ and Crea values. In group 3 (drug) calves, a significant increase was detected in blood pH, Na^+ ($p < 0.01$) and HCO_3^-, Cl^-, BE ($p < 0.05$) values after treatment, while a significant decrease in K^+ and Crea values ($p < 0.05$, $p < 0.01$) was observed. Post-treatment blood gas results among the groups are as follows: a significant increase in pH, HCO_3^- ($p < 0.05$) and BE ($p < 0.01$) was detected in Group 2 calves compared to Group 1, while a significant decrease in K^+ value ($p < 0.05$) was detected. A significant increase in Na^+, BE values ($p < 0.05$), and a significant decrease in K^+ value ($p < 0.05$) were found in Group 2 calves compared to Group 3 (Table 1). In-group results of diarrheal calves according to blood biochemistry values before and after treatment are as follows: In group 1 calves, there was a significant decrease in AST, ALT ($p < 0.05$), and BUN ($p < 0.01$) values after treatment, and a significant increase in glucose value ($p < 0.05$). In group 2 calves, a significant decrease was detected in AST, BUN ($p < 0.01$) and ALT ($p < 0.05$) values, while a significant increase in glucose value ($p < 0.01$) was detected after treatment. After treatment in group 3 calves, a significant decrease in AST, ALT ($p < 0.05$) and BUN ($p < 0.01$) values and a significant increase in glucose value ($p < 0.05$) were detected in calves. No significant difference was found among the blood biochemistry results of the groups after treatment (Table 2). In the feces scores of calves with diarrhea after treatment, a statistically significant improvement at the level of $p < 0.05$ in Groups 1 and 3, and an improvement at the level of $p < 0.01$ in Group 2 were observed (Table 3).

Table 3 - Feces scores of calves with diarrhea before, after treatment and statistical comparison between groups.

Groups	B.T	A.T	Between group comparisons
	Median [25%-75%]	Median [25%-75%]	P
Group 1	1 [1 -2]	3 [3 -4]	*
Group 2	1 [1 -2]	4 [3 -4]	**
Group 3	1.5 [1 -2]	4 [4 -4]	*
Group 4	4 [4 -4]	4 [4 -4]	

* : P < 0.05, ** : P < 0,01, B.T: Before Treatment, A.T: After Treatment
1=watery, 2=pudding consistency, 3=soft, 4=hard

DISCUSSION

Cryptosporidium is particularly common in calves with insufficient immunity, who do not receive sufficient and high-quality colostrum and are exposed to stress such as cold and bad ventilation. Due to the lack of a complete and effective treatment, it is important to evaluate new treatment options. Clinoptilolite has been used by different researchers and its effectiveness in diarrhea cases has been investigated. Panousis et al. reported that clinoptilolite decreases intestinal transit rate, absorbs water, and tightens feces consistency[10]. Sadeghi and Shawrang reported in their study that clinoptilolite added to milk reduced the formation of diarrhea. It has been suggested that this effect is achieved by directly affecting the osmotic pressure in the gastrointestinal system and creating a change in metabolic acidosis[9]. In this study, the effectiveness of clinoptilolite in addition to the standard treatment protocol was investigated in cases of calf diarrhea caused by *Cryptosporidium*.

Kasari[11] associated decreases in pH and HCO_3^- values with metabolic acidosis in 1999. In this study, in the comparisons within groups, it was determined that pH and HCO_3^- values increased significantly in all three groups after treatment. The findings obtained are consistent with the research[12,13]. When the post-treatment values in Groups 1, 2 and 3 were compared, there was no significant difference between Groups 2 and 3, while the difference between Groups 1 and 2 was significant. It was concluded that the clinoptilolite used for supportive medicine contributes to the healing.

In the comparisons within the group, it was observed that Na^+

and Cl^- values increased after treatment. It has been reported that hyponatremia and hypochloremia occurring in diarrhea cases are associated with Na^+ and Cl^- lost by excessive feces and intestinal secretions[14]. However, the data we obtained were similar to the research[12,15]. Başer and Civelek reported[13] in their study in 2013 that there was no significant difference in the amount of Na^+ between healthy calves and calves with diarrhea. In the statistical evaluation after the treatment between the groups, it was found that the Na^+ value of group 2 increased compared to group 3 where only the drug was used. BE values increased in all calves after treatment, and the findings are in parallel with the research[16]. In the statistical evaluation between all groups, a significant difference was found after the treatment.

Blood K^+ concentration increases as fluid and HCO_3^- loss increases in calves with diarrhea[12,17]. Despite the loss of K^+ in diarrhea, the increased concentration in the blood was explained by the replacement of intracellular ion potassium with hydrogen[26]. The data by Awadalla reported[18] that such an increase may be due to oliguria or anuria because the kidneys cannot eliminate excess potassium. It was observed that the intragroup K^+ values decreased after the treatment and the results obtained were found to be compatible with the research[11,12,13]. When the values after treatment in Group 1, 2 and 3 were compared, a significant decrease was found in Group 2 and a statistically significant difference among the three groups.

Urea and creatinine levels increase in cases of infection, high fever, anorexia, and especially dehydration[19]. The reason for the increase in urea and creatinine in diarrhea calves has been explaıned as a decrease in renal perfusion along with dehydration[12]. In the study, it was found that serum creatinine concentration measured in dehydrated neonatal calves before treatment increased statistically after treatment. These findings are similar to the results of different studies[12,20]. When the post-treatment values were compared in groups 1, 2 and 3 no significant difference was found between creatinine levels. It has been reported that the addition of clinoptilolite at different rates to the diets of lambs[21] and chickens[22] did not make a significant difference in creatinine level. These results are in line with our study.

Increased AST activity in serum is a sensitive indicator of liver damage, and the damage is subclinical. In addition, AST enzyme level increases with anterior stomach tension, passive congestion, and muscle breakdown[23]. In this study, it is reported that the pre-treatment AST amount increased in all three groups in accordance with other studies[13,20] in the in-group comparisons, and this may be related to liver damage caused by endotoxemia. When the post-treatment values in groups 1, 2 and 3 were compared, it was concluded that the difference between AST and ALT was not significant and that clinoptilolite had no effect on parenchymatous organs. The results obtained are similar to the results of different research groups[24].

One of the most important complications of diarrhea in calves is hypoglycemia[25]. Since newborns are born with a limited energy reserve, any condition that affects energy intake will result in a disturbance in blood glucose balance[26]. In the study, it was determined that glucose increased statistically in the in-group comparison after treatment. Santos et al. reported in their study in 2002 that Salmonella-infected calves with diarrhea were hypoglycemic[27]. Our study results are in line with the results of other research[28]. When the post-treatment values were compared in groups 1, 2 and 3 no significant difference was found among glucose levels. In their study conducted in 2018, Uyarlar et al. reported that clinoptilolite did not affect blood glucose level in metabolic disease-free cows with similar milk yield up to the twenty-eighth day of lactation[29]. In addition, blood gas and blood biochemistry values obtained after treatment in the study were found to be between physiological values[30].

Feces score was almost the same in the three groups before treatment (median 1-2), while a significant increase was seen after treatment (median 3-4). A statistically significant increase in feces score was found when Group 2 was compared with the other groups. With its ion exchange[9] and toxic agents removal feature[1], clinoptilolite can be viewed as an alternative in the treatment of acute diarrhea and as a supplement to homeostasis.

CONCLUSIONS

As a result, in addition to standard treatment, oral clinoptilolite at a dose of 1 g/kg per day for 5 days can contribute to the treatment of calves with *Cryptosporidium* and its use in calves is safe. Considering the ineffectiveness of drugs used in the treatment of diarrhea caused by *Cryptosporidium* in calves, increasing calf deaths, and economic losses, the use of clinoptilolite can be considered as a strong alternative in increasing treatment success rate. In future studies, it is thought that the effectiveness of clinoptilolite can be demonstrated from different angles by including more infected animals with *Cryptosporidium* diarrhea, using different doses of clinoptilolite, and determining the number of *Cryptosporidium* oocysts in the feces.

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